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Epidemiologic Evidence for Different Roles of Ultraviolet A and B Radiation in Melanoma Mortality Rates

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Abstract

The action spectrum of ultraviolet radiation mainly responsible for melanoma induction is unknown, but evidence suggests it could be ultraviolet A (UVA), which has a different geographic distribution than ultraviolet B (UVB). This study assessed whether melanoma mortality rates are more closely related to the global distribution of UVA or UVB. UVA and UVB radiation and age-adjusted melanoma mortality rates were obtained for all 45 countries reporting cancer data to the World Health Organization. Stratospheric ozone data were obtained from NASA satellites. Average population skin pigmentation was obtained from skin reflectometry measurements. Paradoxically, melanoma mortality rates decreased with increasing UVB in men ($r = -0.48$, $p < 0.001$), and women ($r = -0.57$, $p < 0.001$), and with increasing UVA in both sexes. By contrast, rates were positively associated with increasing UVA/UVB ratio in men ($r = +0.49$, $p < 0.001$) and women ($r = +0.55$, $p < 0.001$). After multiple adjustment that included controlling for skin pigmentation, only UVA was associated with melanoma mortality rates in men ($p < 0.02$), with a suggestive but non-significant trend present in women ($p = 0.l2$). UVA radiation was associated with melanoma mortality rates after controlling for UVB and average pigmentation. The results require confirmation in observational studies.

Key words: Malignant melanoma, epidemiology, ultraviolet A, ultraviolet B, international comparisons, mortality rates

List of Abbreviations

DNA = deoxyribonucleic acid

ERBE = Earth Radiation Budget Experiment

FokI = A polymorphism of the vitamin D receptor gene translation initiation site

NASA = National Aeronautics and Space Administration

PER = photoprotective epidermal response

PTCH = A tumor-suppressor gene possibly involved in nonmelanoma skin cancer

TaqI = A polymorphism of site I3841 on Exon 9 of the vitamin D receptor gene

TP53 = A tumor-suppressor gene possibly involved in nonmelanoma skin cancer

TOMS = Total Ozone Mapping Spectrometer, an satellite-based instrument that measures ozone thickness.

UVA = ultraviolet A radiation (320-400 nm)

UVB = ultraviolet B radiation (295-320 nm)

WHO = World Health Organization

Introduction

There will be 53,600 new melanoma cases and 7,400 deaths in the United States in 2002 (1). Incidence and mortality rates have continued to rise unabated since the 1950s in the United States (2, 3). The epidemiology of melanoma is paradoxical. It has long been suspected that malignant melanoma is associated with exposure to sunlight, and that ultraviolet B (UVB) was the probable causal factor due to its role as the principal factor in reddening and edema of the skin, and its tendency to produce thymidine dinucleotides and other characteristic DNA mutations, (4-6). Unfortunately, the relationship of sunlight exposure with risk of melanoma may be more complicated than suggested by a simple solar exposure model of aetiology. For example, workers engaged in primarily in outdoor occupations tend to have lower incidence rates of melanoma compared with those engaged in indoor occupations (7-9). The odds ratio for heavy sunlight exposure at work during the past 20 years in one case-control study was 0.58 (95% confidence interval, 0.36 to 0.95) (7). Within the United States, incidence rates historically were higher at lower latitudes (10), although incidence rates have been increasing markedly in other areas since the 1950s, particularly the northeast (11, 12). In Europe, incidence and mortality rates are much higher at higher latitudes (7).

Intermittent recreational exposure has been of greater concern. Despite uncertainty about the portion of the solar spectrum involved in the aetiology of melanoma, attempts to prevent melanoma have generally relied on recommendations to use sunscreens that mainly absorb UVB (3, 12, 13).

Historically, it has been thought that the most important action spectrum for human melanoma is solely UVB (14, 15), although a role for ultraviolet A (UVA) has been suspected

(12, 13, 16-20). The reported associations of sunscreen usage with melanoma and other skin cancers could not be explained by predisposing factors such as skin type. Sunlight consists of UVA (315-400 nm), UVB (280-315 nm), visible light, and infrared (21). The preponderance of UVB is absorbed by the ozone layer (22), which is transparent to UVA, visible and infrared irradiation (23). Most of the energy received from the sun at ground level is in the visible and infrared and only a small proportion is in the ultraviolet (23). Historically, it was estimated that 5% of solar UV irradiation was UVB (24). However, more recent spectrophotometric measurements suggest that UVB is approximately 3% of total UV energy at noon in midsummer.

Melanoma incidence rates have increased markedly since 1955 in the United States and many other countries with predominantly Caucasian populations, with a smaller but concomitant rise in age-adjusted mortality rates (25). Melanoma death was once so uncommon in the United States that it was not tabulated separately as a cause of death in vital statistics reports from the US National Center for Health Statistics until 1955 (26). It was instead combined with deaths from squamous and basal cell carcinomas (26). The average rate of increase in melanoma in the United States has been approximately 3% per year since the mid-1950s (27).

The highest rates of melanoma incidence and mortality in the world occur in New Zealand and Australia (28). Melanoma was once uncommon in both countries, but it is now the fourth most common cancer in both, and lifetime risk is now 1 in 25 persons (27). Melanoma was formerly uncommon in northern Europe, but now the highest rates of melanoma in Europe occur in Norway, Denmark, Slovenia, the former Czech Republic, and Sweden (27). The rise in rates of melanoma in Europe occurred first in Northern European countries and later, if at all, in more southern countries (27). Melanoma rates remained low and stable in Italy throughout the period of acceleration of rates in the United States, Australia, New Zealand, and, later, in

northern Europe.

There are a number of genotypic and phenotypic predisposing factors associated with melanoma risk, including having fair skin. People with fair skin are more likely than those with more pigmented skin to experience erythema, edema, and skin discomfort after solar exposure (28, 29), and they are more likely to develop melanoma than those with darker skin (30, 31). There is a strong association between gender and trends in incidence rates by anatomical site, with the greatest increase in melanoma being on the torso in men, and on the lower limbs and, especially in recent years, on the torso in women (32, 33).

One of the most compelling issues in melanoma research is the question of the action spectrum for the disease, specifically whether the lesions are due mainly to the slightly more energetic UVB photons or the far more common UVA photons. This is an essential distinction in making decisions about the formulation of sunscreens and in deciding whether sun lamps, which vary greatly in UVA and UVB energy according to type, are safe or hazardous. The issue of action spectrum has been a subject of debate, with some groups suggesting that the effect of UVA is predominant in human melanoma (12, 13, 16-18, 34, 35) with earlier groups having suggested that UVB is the predominant cause of skin cancer in general, although not necessarily melanoma in particular (14, 15, 36, 37).

Most attention to date has centered on UVB since it is the cause of solar erythema and is readily absorbed by DNA (15), where it produces signature mutations in TP53 and PTCH, two tumor suppressor genes that are thought to play a role in nonmelanoma skin cancer (38). Although UVB flux is much weaker than UVA flux, UVB exposure reliably results in these mutational photoproducts. Signature p53 oligonucleotide mutations that are caused mainly by UVB trigger photoprotective responses in the epidermis, including melanogenesis and DNA

repair (6, 39).

The hypothesis that UVA might be the main cause of human melanoma was described at a consensus conference in 1988 (16). The epidemiological evidence pointing to UVA as the predominant factor in melanoma was subsequently reviewed (12, 34).

The theory of UVA predominance as the causative factor in melanoma was advancing concurrently in the field of experimental carcinogenesis. Setlow and associates reported on a serendipitous natural experiment that demonstrated that melanoma in fish could be induced by filtered sunlight that contained only UVA and visible light (17). The investigators maintained a colony of swordtail platyfish in a greenhouse that excluded UVB. The fish unexpectedly developed melanoma. Fish maintained in a normal opaque structure did not develop the lesions. Setlow's research provided experimental support for the concept that UVA is a cause of melanoma in fish (17). Setlow's findings (17, 18) were in agreement with the hypothesis that UVA was the predominant cause of melanoma (12, 16, 34, 40).

This report adds another dimension to the UVA hypothesis by assessing whether UVA, UVB, or the ratio of UVA to UVB is the best predictor of melanoma, based on analysis of mortality data from 45 countries, with control for confounding by average pigmentation.

Methods

The ultraviolet photon flux for each nanometer in the UVA (320-400 nm) and terrestrial UVB (295-320 nm) were modeled as a function of solar noon zenith angle at different latitudes at the equinoxes. The solar noon zenith angle is the number of degrees that the sun, at its highest point during the day, deviates from the zenith. The zenith is a point in the sky on a line

perpendicular to the Earth's surface. A solar zenith angle of 0 degrees, for example, denotes a position of the sun directly overhead. The solar zenith angle was calculated for March 20 and September 22, the dates of the equinoxes. These are the dates when the equator is parallel to the plane of rotation of the earth around the sun.. At the equinoxes, the noon solar zenith angle is equal to the latitude. For example, in San Diego (33 degrees north), the noon solar zenith angle is 33 degrees. The maximum elevation of the sun above the horizon is 90 degrees minus the solar zenith angle. At solar noon on the equinox dates in San Diego, the maximum solar elevation above the horizon is therefore 90-33 degrees, or 57 degrees. In Boston (42 degrees north) the maximum equinoctial elevation of the sun above the horizon on the dates of the equinoxes is only 48 degrees.

The method used for this study provides an approximate estimate of the photon flux in nanometer or smaller increments. The model took into account the effect of global variations in column ozone, a measure of the thickness of the stratospheric Hartley and Huggins ozone layers, which absorb UVB (41). The model did not take into account the possible effects of cloud cover.

Age-adjusted mortality rates of melanoma were obtained from the World Health Organization (WHO) using the Web site of the International Agency for Research on Cancer (www.iarc-dep.fr). This Web site is the official standard cancer mortality site for the WHO in Geneva, and it is the standard source for cancer mortality data. Each participating country determines mortality rates based on death certificates from the entire country and census data from national censuses. Owing to delays in reporting, the earliest year for which reasonably complete data were available was 1990, and that year was used for the analyses. The rates were reported by WHO by 45 countries. The rates were age-adjusted by WHO to the world standard population and were provided specific for sex.

Regional differences in skin pigmentation among countries were determined using Jablonski-Chaplin average population skin pigmentation codes developed by the California Academy of Sciences, which are based on average population dermal reflectometric measurements. This method is described in detail elsewhere (42). A code of 0 was used in the present study to identify populations with average minimal pigmentation, 1 for moderate pigmentation, 1.5 for moderately dark pigmentation, and 2 for dark pigmentation (42). Column ozone data were obtained from satellite measurements made by the Scripps Institute of Oceanography using data from the NASA Total Ozone Mapping Spectrometer (TOMS) and Earth Radiation Budget Experiment (ERBE) satellites (41).

Correlation coefficients were calculated using the Microsoft® Excel Chart subroutine. The best fit to the data points was obtained using an exponential trend line. Multiple linear regression was performed using InStat Version 3.0 (GraphPad Software , San Diego, CA).

Results

The results are summarized by country in Table 1. Melanoma mortality rates paradoxically decreased with increasing UVB flux in men ($r = -0.48$, $p < 0.001$), and women ($r = -0.57$, $p < 0.001$) (Figures 1-2), and also with increasing UVA flux in men ($r = -0.50$, $p < 0.001$), and women ($r = -0.57$, $p < 0.001$) (Figures 3-4). By contrast, rates were positively associated with increasing UVA/UVB ratio in men ($r = +0.49$, $p < 0.001$) and women ($r = +0.55$, $p < 0.001$) (Figures 5-6). After controlling for skin pigmentation using multiple regression, only UVA was associated with melanoma mortality rates in men ($p < 0.02$), with a suggestive but nonsignificant trend present in women ($p = 0.12$) after adjustment for the effect of pigmentation (Table 2).

Discussion

This ecological research shares several of the limitations of most ecological studies. Findings that apply to aggregates do not necessarily apply at the individual level. While it was possible to control for average skin pigmentation at a countrywide level, it was not feasible to take into account individual behavior patterns that could be addressed in observational studies, including dietary habits, outdoor exercise, travel, migration, and use of tanning lamps.

The data were limited to only 45 of the world's 155 countries that reported data to the International Agency for Research in Cancer, and these were mainly the industrialized countries. Third world countries were underrepresented.

The ultraviolet radiation data were determined based on known measurements at a limited number of sites combined with latitude and ozone layer thickness. Since there are only a few sites with spectrophotometric UV measurements in the world, the data may be imprecise. More spectrophotometer sites clearly are needed in different countries. Since UVA, UVB, the ratio of UVA to UVB, and pigmentation are correlated, assessment of the individual contribution of each variable is difficult. If the variables were entered in a specified order, the first to enter could explain most of the variance. However, these variables were not entered into the regression model in a specified order, and the regression program allowed to assignment of the regression coefficients in the order of explained variance, entering the variable that explained the most variance first. Still, regression with variables that are correlated can be problematic. The purpose of the regression was to identify the independent effects of UVA, UVB, and the UVA/UVB ratio while controlling for pigmentation, though, so it was not feasible to exclude these variables from

the regression model. The UVA hypothesis is based on age-adjusted mortality rates, which are the only rates that are available for countries covering such a broad range of latitudes. Incidence rates, which are not available from most countries, might give a better approximation of risk estimates. However, mortality rates may provide a more certain diagnostic endpoint.

The global distribution of UVA accounts for much of the global variation in mortality rates from melanoma, specifically the unexpectedly high rates in latitudes relatively distant from the equator. The UVA hypothesis accounts for the significantly higher prevalence of melanocytic nevi that was found in children whose parents regularly applied UVB sunscreens to them (43), although another study found a minimal reduction (44). It is consistent that the number of sunburns the child had experienced was not associated with nevus count (43).

Since the action spectrum of melanoma induction in humans is still uncertain, this study examined geographic correlates and a natural experiment for information that might be supportive of either UVA or UVB, or of a combination of the two, as important in melanoma. A pertinent natural experiment was started by the discovery, in 1922, of UVB sunscreens, and their diffusion throughout the population of industrialized countries in the 1950s, first marketed as suntan lotions, and subsequently as sunblocks. The introduction of UVB sunscreens, which allowed much longer exposures to UVA, was accompanied by a marked rise within 15-25 years in age-adjusted incidence rates of melanoma (12).

Only UVA was positively related to melanoma mortality rates in men after controlling for skin pigmentation (Table 2). This is perhaps not completely surprising since 97-98% of UV radiation is UVA (Table 1). The associations between UV radiation and melanoma mortality in Figures 1-6 appear to best fit a quadratic relationship for men, and a linear relationship for women. Possible explanations might be that men spend more time outdoors than women, or they

may expose more surface area than women, such as the entire torso while working or engaging in sports.

It is important to try to delineate the specific roles of UVA and UVB radiation in melanoma because most current sunscreen formulations, which are made with a 2 or 3% solution of oxybenzone, transmit large amounts of UVA. While UVB directly mutates DNA (38), UVA radiation mutates DNA indirectly through free-radical mediated oxidative damage to guanine bases (20). Far more UVA reaches the melanocyte than UVB, based on quantum calculation of wavelength dependence of photons and there is a UVA/UVB photon ratio in solar noon equinoctial sunlight at temperate latitudes in clear sky conditions in clean air of 30-40 UVA photons to each UVB photon (20, 45). Since the epidermal layers overlying the basal layer in Caucasian skin absorb 56% of UVB and 27% of UVB on average (46), the number of UVA photons reaching the melanocyte at noon is 60-80 times greater than the number of UVB photons reaching it, or 98-99% of photons reaching the basal epithelium.

The equinoctial UVA flux at solar noon is about half as high at the Arctic Circle as at the equator. Therefore, there is less UVA present in an absolute sense in the higher latitudes than in the lower. However, the difference in solar noon UVB fluxes between the Arctic Circle and the equator at the equinoxes is much greater, making the UVA/UVB ratio increase with increasing distance from the equator.

The UVA hypothesis also helps to account for the unexpected and paradoxical higher risk of melanoma in regular users of UVB sunscreens that has been reported in several epidemiologic studies, since most sunscreens provide little protection against UVA. Eight epidemiologic studies have reported that regular use of sunscreens is associated with significantly increased risk of melanoma (19, 47-53). The association persisted after controlling

for the amount of time spent in the sun, skin type, and other predisposing factors, including history of sunburns. Five of these studies reported higher risk of melanoma associated with use of sunscreens in both sexes (19, 49, 50, 52, 53), while three reported the association in men (47, 48, 51). Another study reported a higher incidence of nevi, pigmented benign lesions of the epidermis that are associated with increased risk of melanoma, in children whose parents regularly applied sunscreens to the children's skin when outdoors in the sun (43).

A large cohort study of nurses reported that among women who spent at least 8 hours per week outdoors during the summer, regular use of sunscreens was associated with significantly increased risk of basal (54) and squamous (55) cell carcinoma. The increased incidence of both types of skin cancer associated with use of sunscreens persisted after adjusting for age, self-reported sensitivity to sunlight, and history of sunburns. By contrast, three case-control studies were identified, including two from Spain and one from the United States (56-58), that reported an apparently favorable association of sunscreen use with risk of melanoma.

There are few animal models for the induction of melanoma. The fish model is *Xiphophorus*, a swordtail-platyfish hybrid (17). The action spectrum for a melanocytic tumor resembling or possibly the same as melanoma in fish includes three peaks in the UVA, with a prominent peak at 365 nm (17, 18, 35). If the fish model is applicable to humans, convolution of the solar spectrum with the action spectrum for the fish model suggests that 90% of human melanoma is due to UVA (17). The other known animal model of melanoma is the miniature opossum, *Monodelphis domestica*. Some adults of these animals develop melanoma upon prolonged exposure to mixed UVB-UVA radiation (59). A study of infant opossums revealed a single melanoma precursor lesion after exposure to UVA (59), in 1 of 70 animals exposed on 9 occasions to 250 MJ/m^2 UVA.

Jablonsky-Chaplin population average skin pigmentation, which was used as a control variable in this study, was developed based on a systematic review of dermal reflectometry readings that were reported from a wide range of anthropological studies (42).

Mechanisms. UVB-induced mutations (thymidine dinucleotides) in the normal, solar unaccommodated epidermis are thought to stimulate a photoprotective epidermal response (PER) that includes synthesis and release of melanosomes by melanocytes (6, 39) (Figure 7). This reduces penetration of UV radiation to the basal epidermis and melanocytes (Figure 8). There is also proliferation of the keratinocytes, leading over a period of days to weeks to thickening of the stratum corneum, an adaptation that tends to help scatter UV radiation, also reducing the penetration of UV radiation (Figure 8).

When the skin is exposed to UVA alone in dosages similar to those in sunlight, the stratum corneum does not thicken appreciably, relatively little melanin is synthesized, that which is produced is only partially oxidized, and pigmentation is relatively weak.

Terrestrial UV radiation contains vastly more UVA energy then UVB energy, particularly at high latitudes. Sunscreen use or ordinary solar exposures at high latitudes where UVB flux is low, diminishes the natural PER due to UVB exposure. As a result, the basal epithelium, including the melanocytes, is exposed to a relatively large flux of UVA photons. UVA photons activate free radicals that damage the DNA through oxidative damage to guanine bases (13, 20). The ultimate result is mutation of the DNA and promotion of melanoma through a series of mutations of proto-oncogenes or tumor suppressor genes (13, 20).

Caution should be associated with any exposure of the skin to radiation where the ratio of UVA to UVB is higher than normally encountered in ordinary sunlight. Such exposures commonly are produced by application of sunscreens, which allow prolonged UVA exposure.

Few sunscreens contain true broad-spectrum blockers in effective concentrations, such as titanium dioxide or zinc oxide. The current sun protection factor for sunscreens has no relationship to the efficiency of removal of UVA photons.

UVB appeared to be associated with lower melanoma mortality rates in women and borderline effects in men when UVA and average population skin pigmentation were included in the regression (Table 2). This association could be due to chance, or could be product of regression modeling. However, the effect also is consistent with the role of UVB in stimulating photoprotective accommodation of the skin. A further possibility is that UVB, which is unique in stimulating synthesis of vitamin D from 7-dehydrocholesterol in skin, may exert a beneficial effect of risk of melanoma through a mechanism involving vitamin D synthesis. Vitamin D metabolites reduce proliferation in certain human melanoma cell lines (60). Individuals with mutations of the vitamin D receptor FokI site are at higher than average risk of developing melanoma (61), and those with mutations of the vitamin D receptor FokI and TaqI sites had melanomas with deeper than average Breslow thickness and poorer prognosis at the time of diagnosis (61), suggesting a role of the vitamin D system in melanoma.

Additional research is needed to more fully investigate the UVA hypothesis and to further define the roles of the PER and vitamin D metabolites and receptors in melanoma. Observational studies of individuals are needed to confirm the results of these ecological analyses.

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Figure Legends **(No figures provided with the report)**

Figure 1. Age-adjusted melanoma mortality rates by UVA flux, men

Figure 2. Age-adjusted melanoma mortality rates by UVA flux, women

Figure 3. Age-adjusted melanoma mortality rates by UVB flux, men

Figure 4. Age-adjusted melanoma mortality rates by UVB flux, women

Figure 5. Age-adjusted melanoma mortality rates by UVA/UVB ratio, men

Figure 6. Age-adjusted melanoma mortality rates by UVA/UVB ratio, women

Figure 7. Epidermis without solar accommodation allows considerable penetration of UVA and UVB

Figure 8. Solar-accommodated epidermis, showing melanin pigmentation of the epidermis, thickening of the stratum corneum, and reduced penetration of UVA and UVB

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14. ABSTRACT (maximum 200 words) **The action spectrum of ultraviolet radiation mainly responsible for melanoma induction is unknown, but evidence suggests it could be ultraviolet A (UVA), which has a different geographic distribution than ultraviolet B (UVB). This study assessed whether melanoma mortality rates are more closely related to the global distribution of UVA or UVB. UVA and UVB radiation and age-adjusted melanoma mortality rates were obtained for all 45 countries reporting cancer data to the World Health Organization. Stratospheric ozone data were obtained from NASA satellites. Average population skin pigmentation was obtained from skin reflectometry measurements. Paradoxically, melanoma mortality rates decreased with increasing UVB in men ($r = -0.48$, $p < 0.001$), and women ($r = -0.57$, $p < 0.001$), and with increasing UVA in both sexes. By contrast, rates were positively associated with increasing UVA/UVB ratio in men ($r = +0.49$, $p < 0.001$) and women ($r = +0.55$, $p < 0.001$). After multiple adjustment that included controlling for skin pigmentation, only UVA was associated with melanoma mortality rates in men ($p < 0.02$), with a suggestive but nonsignificant trend present in women ($p = 0.l2$). UVA radiation was associated with melanoma mortality rates after controlling for UVB and average pigmentation. The results require confirmation in observational studies.**

15. SUBJECT TERMS
Vitamin D, ultraviolet radiation, melanoma, ozone, ultraviolet A (UVA), ultraviolet B (UVB), skin pigmentation, epidemiology

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